SYNTHESIS OF A 16-MEMBERED N,S-CONTAINING MACROHETEROCYCLE INCLUDING SERINE AND HISTIDINE FRAGMENTS. SYNTHETIC MODEL OF THE ENZYME α-CHYMOTRYPSIN

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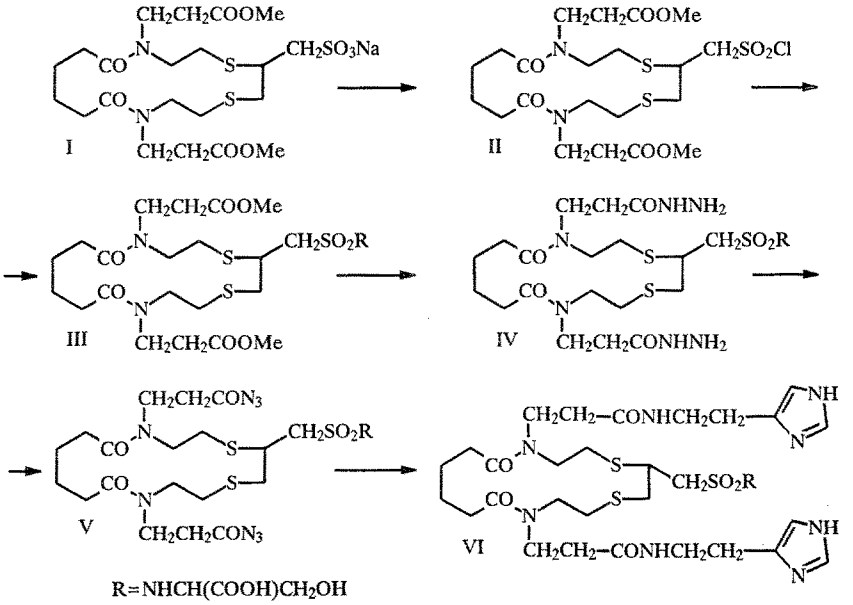
Macroheterocycles that contain catalytically active functional groups are of interest as low-molecular-weight models of enzymes ("synzymes") [1, 2].

We have previously obtained polyfunctional nitrogen- and sulfur-containing crown compounds and their complexes with the Cu(II) ion [3-5]. The spectral characteristics and redox potentials of these complexes provide evidence for their similarity to the active center of "blue" proteins [6].

Continuing our development of methods for the synthesis of new types of macroheterocycles that have the properties of "synzymes" we obtained crown compound VI with exocyclic hydroxy, carboxy, and imidazolyl groups. Structurally and functionally, macroheterocycle VI is a model of the enzyme α-chymotrypsin, the catalytic activity of which is due first and foremost to the serine and histidine fragments present in its active center [7].



The reaction of crown compound I [3] with $SOCl_2$ in DMF leads to sulfonyl chloride II [an oil, 80% yield. IR spectrum (KBr): 1720 ($COOCH_3$); 1640 (CON); 1380, 1180 cm^{-1} (SO_2). PMR spectrum (d_6-DMSO), δ: 2.51 (m, CH_2), 2.73 (m, SCH_2), 2.88 (m, NCH_2), 3.64 ppm (s, OCH_3)]. The latter reacts with L-serine in DMF at 0°C to give crown compound III [75% yield, mp 125-126°C. IR spectrum (KBr): 2600, 2490 (COOH); 1730 ($COOCH_3$); 1640 (CON); 1380, 1180 cm^{-1} (SO_2). PMR spectrum (d_6-DMSO), δ: 2.64 (m, CH_2), 2.75 (m, SCH_2), 2.90 (m, NCH_2), 3.24 (s, OH), 3.74 ppm (s, OCH_3)]. The reaction of hydrazine hydrate with macroheterocycle III in dry ethanol leads to dihydrazide IV (82%

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yield, mp 300°C). Treatment of macroheterocycle IV with $NaNO_2$ leads to unstable diazide V, which, without prior purification, is subjected to reaction with histamine in DMF at room temperature. The resulting 1,4-dithia-7,14-diazacyclohexadecane VI is a light-green crystalline substance that is soluble in ethanol, DMF, and DMSO [75% yield, mp 170-171°C. IR spectrum (KBr): 3130 (associated NH, OH); 2400-2800 (COOH); 1660 (C=C, C=N); 1620 (CON); 1380, 1160 cm^{-1} (SO_2). PMR spectrum (d_6-DMSO), δ: 2.58 (m, CH_2), 2.74 (m, SCH_2), 2.92 (m, NCH_2), 3.25 ppm (s, OH)].

The results of elementary analysis of II-VI are in agreement with the calculated values.

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